Tight glycemic control may favor fibrinolysis in patients with sepsis*

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Objective: **To investigate whether tight glycemic control, in patients with sepsis, may restore a normal fibrinolysis by lowering plasminogen activator inhibitor (PAI)-1 levels.**

Design: **Prospective randomized clinical trial.**

Setting: **Three Italian university hospital intensive care units.**

Patients: **Ninety patients with severe sepsis/septic shock.**

Interventions: **Patients were randomized to receive either tight glycemic control (treatment group, target glycemia, 80–110 mg/dL) or conventional glycemic control (control group, target glycemia, 180–200 mg/dL).**

Measurements: **Inflammation, coagulation, and fibrinolysis markers were assessed, along with Sepsis-related Organ Failure Assessment scores, >28 days.**

Main Results: **In the whole population, at enrolment, inflammation and coagulation were activated in >80 of 90 patients, whereas fibrinolysis, as assessed by PAI-1 activity and concentration, was impaired in only 34 patients. The extent of the inflammatory reaction or of the coagulation activation was unrelated to outcome. In contrast, 90-day mortality rate of the 34 patients in whom fibrinolysis was definitely inhibited at study entry was twice that of the 56 patients in whom fibrinolysis was intact (44% vs. 21%, $p = 0.02$). After randomization, during the study, daily glycemia averaged 112 ± 23 mg/dL in the treatment group and 159 ± 31 mg/dL in controls ($p < 0.001$), with total daily administered insulin 57 ± 59 IU and 36 ± 44 IU, respectively ($p < 0.001$). A small, but significant, enhancement of fibrinolysis could be observed in the treatment group, as indicated by the time course of PAI-1 activity ($p < 0.001$), PAI-1 concentration ($p = 0.004$), and plasmin–antiplasmin complexes ($p < 0.001$). Morbidity, rated with the Sepsis-related Organ Failure Assessment score, became significantly lower ($p = 0.03$) in the treatment group.**

Conclusions: **Fibrinolysis inhibition, in severe sepsis/septic shock, seems to have a relevant pathogenetic role. In this context, tight glycemic control seems to reduce, with time, the fibrinolytic impairment and morbidity. (Crit Care Med 2009; 37:424–431)**

KEY WORDS: sepsis; shock; septic; fibrinolysis; plasminogen activator inhibitor 1; blood glucose; tight glucose control

Severe sepsis and septic shock are marked by a widespread, whole-body, inflammatory reaction (1). The associated cytokine-induced coagulation abnormalities (2) responsible for the formation of microthrombi in the microcirculation (3) are one of the possible mechanisms underlying organ failure and death (4). However, inhibition of the global inflammatory reaction (5, 6) of specific inflammatory cytokines (7–14) or of the coagulation cascade (15) did not achieve any survival benefit. Less attention has been paid to the role of the fibrinolytic pathway in sepsis. Although fibrinolysis is impaired in the septic state (16, 17), its part in determining clinical severity is still undefined, and interventions specifically aimed at reactivating it have not been investigated.

The idea for this trial originated from two studies describing survival improvement in patients with sepsis treated with recombinant human activated protein C (18) or undergoing a strategy of tight control of blood glucose to maintain euglycemia (19). Although subsequent studies could not confirm the benefits of recombinant human recombinant activated protein C and tight glycemic control on outcome (20, 21), the possible mechanism by which both interventions acted remained unclear. We wondered whether recombinant human activated protein C and tight glycemic control may share a common mechanism, i.e., reactivation of fibrinolysis as a consequence of lower levels of plasminogen activator inhibitor (PAI)-1, the most powerful endogenous inhibitor of fibrinolysis. In fact, in patients with diabetes (22, 23), hyperglycemia/insulin resistance are powerful inhibitors of fibrinolysis, boosting the concentration and activity of PAI-1. Recombinant human activated protein C, besides having anti-inflammatory and anticoagulant properties (24, 25), is also a powerful suppressor of PAI-1 (26, 27). A possible common mechanism for the beneficial effect of both glycemic control and recombinant human activated protein C might, therefore, lie in the decrease in PAI-1 concentration/activity and the consequent reactivation of fibrinolysis. This mechanism is likely to be maximally effective in full-blown sepsis, when both inflammation and coagulation are massively activated, microthrombi

***See also p. 741.**

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have already formed, and fibrinolysis is significantly impaired. In these conditions, reactivation of the fibrinolytic system could theoretically restore end-organ perfusion. Therefore, in this multicenter randomized clinical study, we primarily investigated the fibrinolyitic pathway in patients with severe sepsis and septic shock and its relationship with tight glycemic control.

METHODS

Participants. Patients were studied from December 2004 to March 2007 at three university hospitals. The study was approved by the institutional review boards of each hospital, and written consent was delayed until the patient had recovered from the effects of sedation. Patients were enrolled if they met previously described criteria (28, 29) for severe sepsis or septic shock. Exclusion criteria were 1) age <16 years; 2) hematologic malignancies or previous bone marrow transplantation; 3) type I diabetes mellitus; and 4) likelihood of early death because of the underlying disease.

Study Design. The primary end point of this study was to investigate whether prevention of hyperglycemia using a strategy of tight control of blood glucose concentration, as opposed to a conventional one, improved fibrinolysis by reducing PAI-1 concentration/activity. Secondary end points were to investigate the effects of this strategy on organ dysfunction and intensive care unit and 90-day mortality.

Patients were randomized to either tight glycemic control (treatment group, 45 patients) or conventional glycemic control (control group, 45 patients) for the entire study period. Patients were allocated by block randomization and stratified, according to the clinical decision of the attending physician, to receive recombinant human activated protein C or not.

Glucose control and insulin treatment in the two groups was performed as described by Van den Berghe et al (19). Target glycemia, measured at least every 4 hours, was 80 and 110 mg/dL in the treatment group and between 180 and 200 mg/dL in the control group.

Data Collection. The study lasted 28 days. Data were collected daily for the first 7 days, every second day until day 13, and then every fifth day until the end of the study or until discharge or death if they occurred early.

Laboratory Measurements. Circulating levels of interleukin-6, C-reactive protein, and tumor necrosis factor-α were measured as markers of inflammatory activation. Prothrombin fragments 1 + 2 and thrombin-antithrombin complexes, both reflecting the amount of generated thrombin, were measured as biochemical markers of coagulation activation. Concentration and activity of PAI-1 and plasma levels of tissue plasminogen activator [using an assay detecting it mainly when complexed to PAI-1, thus indirectly reflecting PAI-1 levels themselves (30)] were determined as markers of fibrinolytic inhibition (the higher levels corresponding to greater inhibition); plasmin–antiplasmin complexes and D-dimer levels were measured as markers of fibrinolytic activation (the latter also reflecting fibrin generation). The 5th and 95th percentiles of the distribution of the values of each investigated variable, as measured in a population of 50 normal subjects (age and gender-matched to the study population), were considered as the upper and lower boundaries of the normality range for each variable. *Post hoc*, we defined as patients with inhibited fibrinolysis the ones in whom both PAI-1 activity and PAI-1 concentration were above the normal ranges.

Each patient's PAI-1 promoter gene, thrombin-activatable fibrinolysis inhibitor gene, and angiotensin-converting enzyme gene genotypes were assessed by polymerase chain reaction. All the aforementioned genotypes were evenly distributed between the two randomization groups. Because no relationships were found between genotypes and phenotype expression, response to therapy, morbidity, and mortality, the polymorphism analysis will not be considered further here (31).

Statistical Analysis. All data were analyzed on an intention-to-treat basis using SAS, version 8.2 (SAS Institute, Cary, NC). Comparisons between treatment groups have been car-

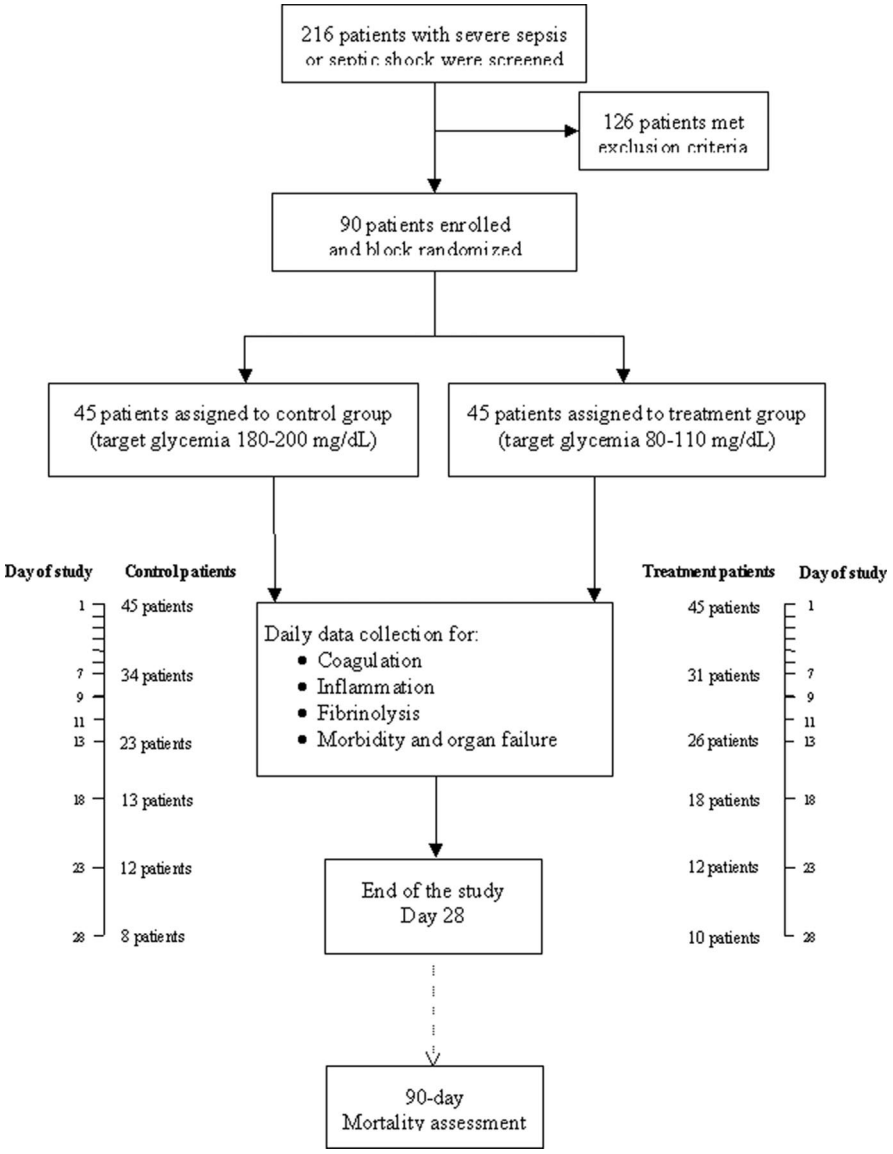

Figure 1. Study flow-chart. Beside the line representing each study day (1–28), we indicated the number of control and treatment group patients remaining in the study at days 1, 7, 13, 18, 23, and 28. At these same time points, 0, 3, 3, 6, 6, and 7 patients died in the control group and 0, 4, 5, 7, 7, and 8 in the treatment group. The patients who were neither dead nor in the study were discharged alive from the intensive care unit to another hospital ward.

Table 1. Characteristics of the study population and profile of biochemical markers of inflammation, coagulation, and fibrinolysis at baseline[a]

Variable	Whole Population (n = 90)	Treatment Group (n = 45)	Control Group (n = 45)	p^b
Males, n (%)	56 (62)	24 (53)	32 (71)	0.08
Age (yrs)	61 ± 15	58 ± 15	64 ± 14	0.07
BMI (kg/m^2)	26.4 ± 6.4	26.5 ± 7.9	26.2 ± 4.6	0.85
ICU admission, n (%)				
Medical	56 (62.2)	30 (66.7)	26 (57.8)	0.38
Surgical	34 (37.8)	15 (33.3)	19 (42.2)	0.38
Infection site, n (% of patients in the category)				
Pulmonary	39 (43.3)	21 (46.7)	18 (40.0)	0.52
Abdominal	28 (31.1)	13 (28.9)	15 (33.3)	0.65
Urinary tract	9 (10.0)	4 (8.9)	5 (11.1)	1.00
Other	20 (22.2)	11 (24.4)	9 (20.0)	0.61
Comorbidities, n (% of patients in the category)				
Hypertension	37 (41.1)	21 (46.7)	16 (35.6)	0.28
Ischemic heart disease	4 (4.4)	2 (4.4)	2 (4.4)	1.00
Heart failure	3 (3.3)	1 (2.2)	2 (4.4)	1.00
Diabetes mellitus (type 2)	12 (13.3)	6 (13.3)	6 (13.3)	1.00
Pancreatitis	3 (3.3)	2 (4.4)	1 (2.2)	1.00
Liver failure	14 (15.6)	5 (11.1)	9 (20.0)	0.24
COPD	18 (20.0)	8 (17.8)	10 (22.2)	0.60
Chronic renal failure	8 (8.9)	4 (8.9)	4 (8.9)	1.00
Severe sepsis, n (%)	59 (65.6)	32 (71.1)	27 (60.0)	0.27
Septic shock, n (%)	31 (34.4)	13 (28.9)	18 (40.0)	0.27
SAPS II score	42.5 ± 14.8	40.8 ± 15.1	44.1 ± 14.5	0.30
SOFA score	10.5 ± 3.6	10.7 ± 3.5	10.3 ± 3.7	0.58
Blood glucose (mmol/L)	9.3 ± 4.8	9.7 ± 5.6	8.9 ± 4.1	0.48
CRP (μg/mL)[c] (norm: 0.15–6.55)	200.18 ± 128.68	201.88 ± 104.66	198.49 ± 150.11	0.90
IL-6 (pg/mL)[c] (norm: 0.19–1.00)	265.88 ± 207.65	275.55 ± 217.38	256.21 ± 199.44	0.66
TNF-α (pg/mL)[c] (norm: 3.75–18.25)	78.73 ± 127.07	72.62 ± 107.85	84.83 ± 144.76	0.65
F_{1+2} (pmol/L)[c] (norm: 89.55–341.09)	398.47 ± 215.35	409.62 ± 237.86	387.34 ± 192.29	0.63
TAT (ng/mL)[c] (norm: 1.05–4.02)	13.47 ± 35.04	16.70 ± 48.54	10.24 ± 10.25	0.39
PAI-1 concentration (ng/mL)[c] (norm: 1.22–31.49)	41.51 ± 52.53	32.13 ± 40.31	51.11 ± 61.64	0.09
PAI-1 activity (IU/mL)[c] (norm: 0.20–18.03)	41.26 ± 41.79	38.83 ± 38.61	43.68 ± 45.05	0.58
tPA (ng/mL)[c] (norm: 2.97–14.93)	22.66 ± 49.43	16.32 ± 14.05	29.00 ± 68.28	0.23
PAP (μg/L)[c] (norm: 199.40–555.40)	785.79 ± 641.07	728.30 ± 514.02	843.28 ± 748.53	0.40
D-dimer (ng/mL)[c] (norm: 86.80–649.20)	8879.79 ± 9856.56	8263.35 ± 9512.16	9496.24 ± 10259.29	0.56

COPD, chronic obstructive pulmonary disease; SAPS II, Simplified Acute Physiological Score—2nd version; SOFA, Sepsis-related Organ Failure Assessment; CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tissue necrosis factor-α; F_{1+2}, prothrombin fragments 1 + 2; TAT, thrombin–antithrombin complexes; PAI-1, plasminogen activator inhibitor-1; tPA, tissue plasminogen activator; PAP, plasmin–antiplasmin complexes; BMI, body mass index (weight in kilograms divided by the square of the height in meters); ICU, intensive care unit.

[a]Plus-minus values are mean ± SD; [b]p values for the difference between treatment and control groups were calculated using Student's t test, χ^2 test, or Fisher's test, as appropriate; [c]range of normal values for each biochemical marker in the laboratory in which performed their analysis.

ried out using Student's t test and chi-square test (or Fisher's exact test) for quantitative and qualitative variables, respectively.

The relationship between outcome and the baseline variables (coagulation, inflammation, and fibrinolysis) has been assessed by survival analysis (log-rank test).

Differences over time between treatment and control groups for each variable were investigated by using analysis of covariance for repeated measures according to a mixed model with treatment (tight or conventional glucose treatment) and time-fixed effects; baseline value of each variable has been included as covariate for adjusting for baseline variability. Variables were natural log-transformed for analyses. p values of <0.05 were considered as statistically significant. p values refer to the trajectory >28 days and not to the differences of means at any given time point, which, instead, were analyzed using Student's t test without any correction for multiple comparisons. As these analyses have been obtained under the assumption of missing at random, their results have to be considered with some caution.

To demonstrate an effect size of 0.30 between the two treatment groups at a statistical significance of 0.05 (two-tailed) and a power of 0.80 (at least) with an unpaired Student's t test, 40 patients per group were required; 45 patients were enrolled to account for 10% dropout rate.

RESULTS

A total of 216 patients were screened, and 90 of them were eligible to be included in the study (Fig. 1). Forty-five patients were randomized to the treatment group and 45 to the control group. Human recombinant activated protein C was given to 12 patients in the treatment group and to 10 controls ($p = 0.62$). Because this cotreatment did not affect any of the primary or secondary end points, for sake of clarity, it will not be discussed any further. Table 1 summarizes the clinical characteristics of the study population and the baseline profile of the biochemical markers of inflammation, coagulation, and fibrinolysis. At enrolment, treatment and control groups did not differ in any of the considered variables. However, in the control group, PAI-1 concentration tended to be higher ($p = 0.09$), the patients included tended to be older ($p = 0.07$), and more men were included ($p = 0.08$) than in the treatment group. The genetic polymorphisms we investigated were similarly distributed between the two groups.

Fibrinolysis Inhibition and Outcome. It is worth noting that fibrinolysis was inhibited in only a fraction of patients with sepsis. The clinical effects of fibrinolysis inhibition are summarized in Figure

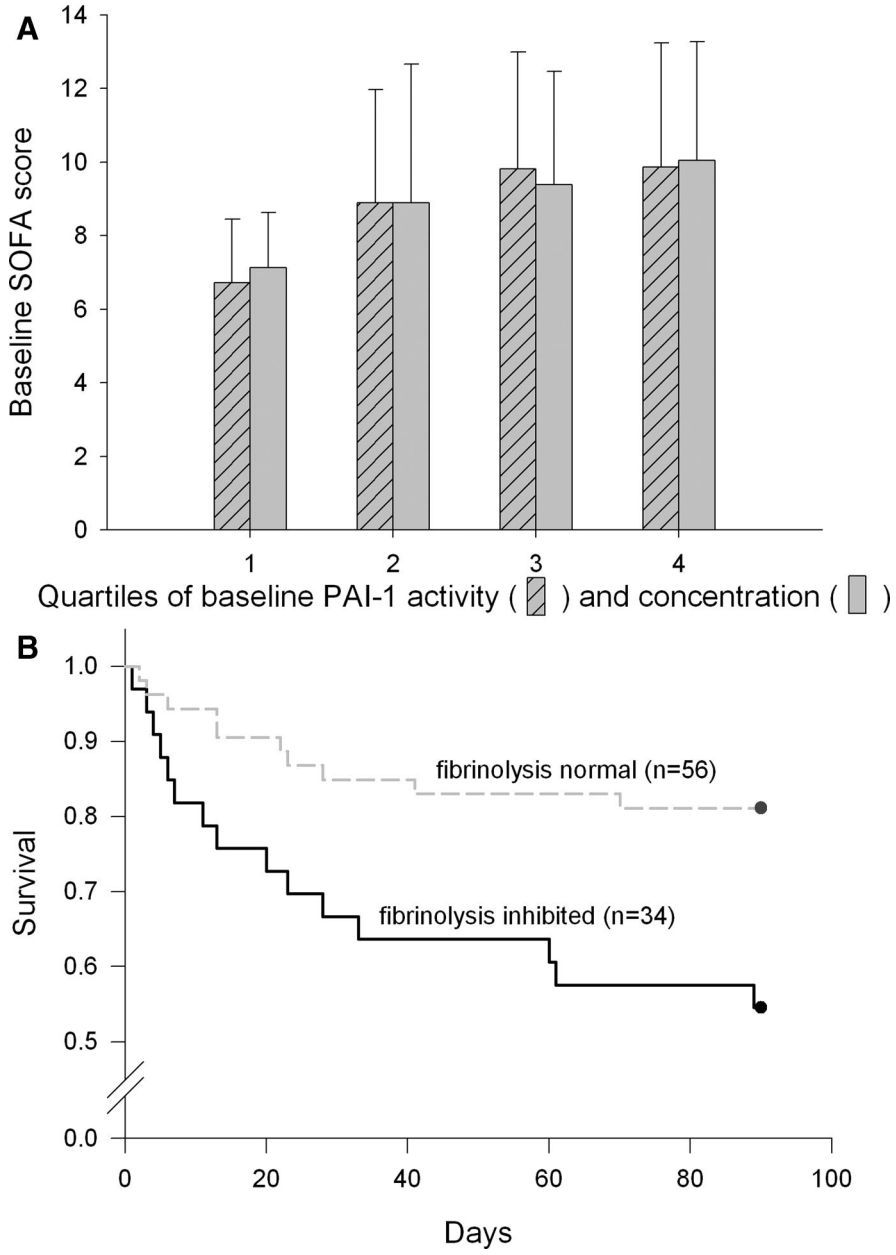

Figure 2. *A*, Sepsis-related Organ Failure Assessment (*SOFA*) scores, measured at study entry in patients grouped according to quartiles of baseline plasminogen activator inhibitor (*PAI*)-1 activity and concentration. Data refer to the whole population. PAI-1 activity and concentration were, respectively, 4.65 ± 1.84 IU/mL and 4.71 ± 1.89 ng/mL for the first quartile, 15.06 ± 5.94 IU/mL and 11.92 ± 3.02 ng/mL for the second, 42.50 ± 13.23 IU/mL and 33.43 + 10.58 ng/mL for the third, and 103.96 ± 30.04 IU/mL and 116.35 ± 56.52 ng/mL for the fourth. Each subgroup included 22 of 23 patients. Higher average PAI-1 activity and concentration are associated with higher SOFA scores ($p < 0.001$ and $p = 0.002$, respectively). The regression between the individual baseline SOFA scores and PAI-1 concentration and activity data, points were also significant ($r^2 = .13$, $p = 0.0006$ and $r^2 = .10$, $p = 0.0018$, respectively). *B*, Kaplan–Meier survival curves of patients with inhibited fibrinolysis (34 patients, *continuous line*) or normal fibrinolysis (56 patients, *broken line*) at study entry. Inhibited fibrinolysis was arbitrarily defined by higher than normal levels of both PAI-1 activity (normal: 0.20–18.03 IU/mL) and concentration (normal: 1.22–31.49 ng/mL). As shown, patients with inhibited fibrinolysis had greater mortality rate than patients with (log-rank $p = 0.005$).

2. At entry, greater levels of fibrinolysis inhibition, as assessed with quartiles of average PAI-1 activity and concentration (Fig. 2*A*), were associated with greater morbidity. Survival probabilities (Fig. 2*B*) were significantly lower for the 34 patients whose fibrinolysis, at study entry, was definitely inhibited (i.e., higher-than-normal PAI-1 activity and concentration levels) than for the other 56 patients (log-rank $p = 0.005$).

Effects of Tight Glycemic Control on Fibrinolysis and Outcome. In the treatment group, average daily blood glucose values (112 ± 23 mg/dL) were significantly lower than in the control group (159 ± 31 mg/dL), as shown in Figure 3*A*; patients in the treatment group received higher daily dosages of insulin, which averaged 57 ± 59 IU, as opposed to 36 ± 44 IU, in the control group ($p < 0.001$). The frequency of hypoglycemic episodes in the two groups is depicted in Figure 4*B*. No neurologic consequences were observed.

The effects of tight glycemic control on the fibrinolytic pathway are reported in Figure 4, where they are compared with those of the conventional approach (*p* values, for this analysis, refer to treatment by time interaction). All markers of fibrinolysis inhibition, PAI-1 activity ($p < 0.001$), PAI-1 concentration ($p = 0.004$), and tissue plasminogen activator ($p = 0.01$), slightly, but significantly, decreased, with time, more in the treatment group than in the control group (Fig. 4*A–C*, respectively). Plasmin–antiplasmin complexes, a marker of fibrinolysis activation, were significantly higher in the treatment group than in the controls ($p < 0.001$, not shown), whereas D-dimer was not significantly different between the two groups ($p = 0.36$, not shown). Sepsis-related Organ Failure Assessment scores also became significantly lower in the treatment group than in the controls ($p = 0.03$), with a time course similar to the decrease in PAI-1 concentration/activity (Fig. 3*D*). Although we observed, with tight glycemic control, a significant decrease in morbidity, as assessed with Sepsis-related Organ Failure Assessment score, we did not find effects of treatment on mortality, which was, respectively, 20% and 18% in the intensive care unit ($p = 0.79$) and 31% and 29% at 90 days from discharge ($p = 0.82$) in the treatment and control groups.

Effects of Tight Glycemic Control on Inflammation and Coagulation. Although tight glycemic control was associated with enhanced fibrinolysis, there were no effects on the activation of coagulation. Thrombin–antithrombin complexes and prothrombin fragments 1 + 2 levels were abnormally elevated at baseline (Table 1) and dropped with time in a similar way in both groups ($p = 0.73$ and $p = 0.56$). The inflammatory cytokines

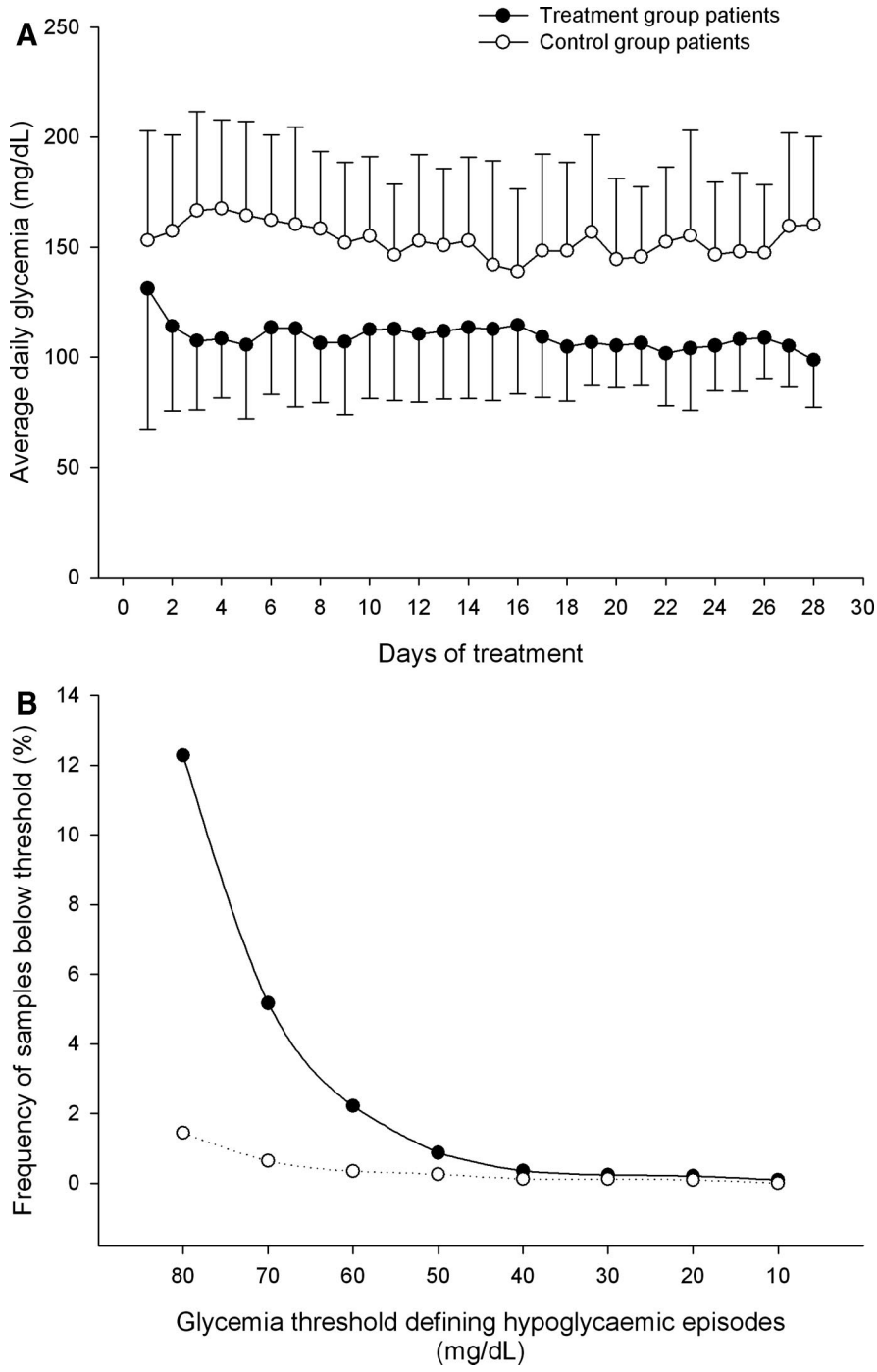

Figure 3. *A*, Daily glycemia in the treatment (*closed circles*) and control group (*open circles*) (mean ± SD). On any given day except baseline, glycemia in the treatment group was significantly lower than in the control group. *B*, Frequency of blood samples (*vertical axis*) with glycemia below the threshold (*horizontal axis*) in the treatment (*closed circles*) and control group (*open circles*). There were 2102 samples for the treatment group and 2113 for the controls. As an example, if 60 mg/dL is chosen as the threshold for hypoglycemia, hypoglycemic episodes were detected in 2.14% of the treatment group samples and 0.33% of the control samples. This means 45 hypoglycemic episodes were recorded in the treatment group compared with only 7 in the control group.

were all abnormally elevated at baseline (Table 1) and decreased with time. Interestingly, interleukin-6 decreased more significantly ($p < 0.001$) in the treatment group than the control group.

DISCUSSION

In this trial, fibrinolysis was inhibited, at entry, only in about 40% of our patients with sepsis or septic shock. However, this inhibition was strongly associated with morbidity and mortality. In this context, a tight glycemic control strategy, as opposed to a conventional one, favored fibrinolysis by lowering PAI-1 concentration/activity and significantly reduced morbidity.

Impaired fibrinolysis during sepsis has been associated with widespread activation of coagulation (2, 4) and with release of inflammatory cytokines (1). In addition, our results suggest that hyperglycemia/insulin resistance may contribute to the inhibition of fibrinolysis not only in chronic disease, as was previously described for diabetes, but also in acute settings. In fact, we found that the strategy of tight control of glycemia in sepsis reduced the inhibition of the fibrinolytic system. The clinical consequences depend on the extent to which the impairment of fibrinolysis is responsible for organ failure and outcome, on the degree to which the reactivation of fibrinolysis can reverse organ failure, and, finally, on the clinical "price" that has to be paid for tight glycemic control.

Several lines of evidence indicate that persistent or worsening coagulopathy in sepsis is associated, to different degrees, with increases in morbidity and mortality (32–35). A pathogenic role has been attributed to high PAI-1 in worsening mortality in acute respiratory distress syndrome (36), and, in severely febrile patients, fibrinolysis impairment was associated with morbidity and mortality more than the activation of coagulation (37). In our patients too, we found that fibrinolysis inhibition was associated with morbidity and mortality (Fig. 2), whereas coagulation activation was not. At entry, only a small proportion of patients (34 of 90) had inhibition of fibrinolysis (abnormally high PAI-1 activity and concentration), and their 90-day mortality rate was 44%, when compared with 21% of the 56 patients in whom fibrinolysis was intact ($p = 0.02$). This suggests that inhibition of fibrinolysis is not a "universal" marker of sepsis, like inflammation/coagulation markers, which are abnormally elevated in virtually all patients with sepsis; instead, it has a pathogenic role leading to more severe disease (38, 39). It is tempting to speculate that, in sepsis, for a given level of microthrombi formation in the microcirculation, what accounts for overall clinical severity is the possibility of dissolution of microthrombi by an intact fibrinolytic system.

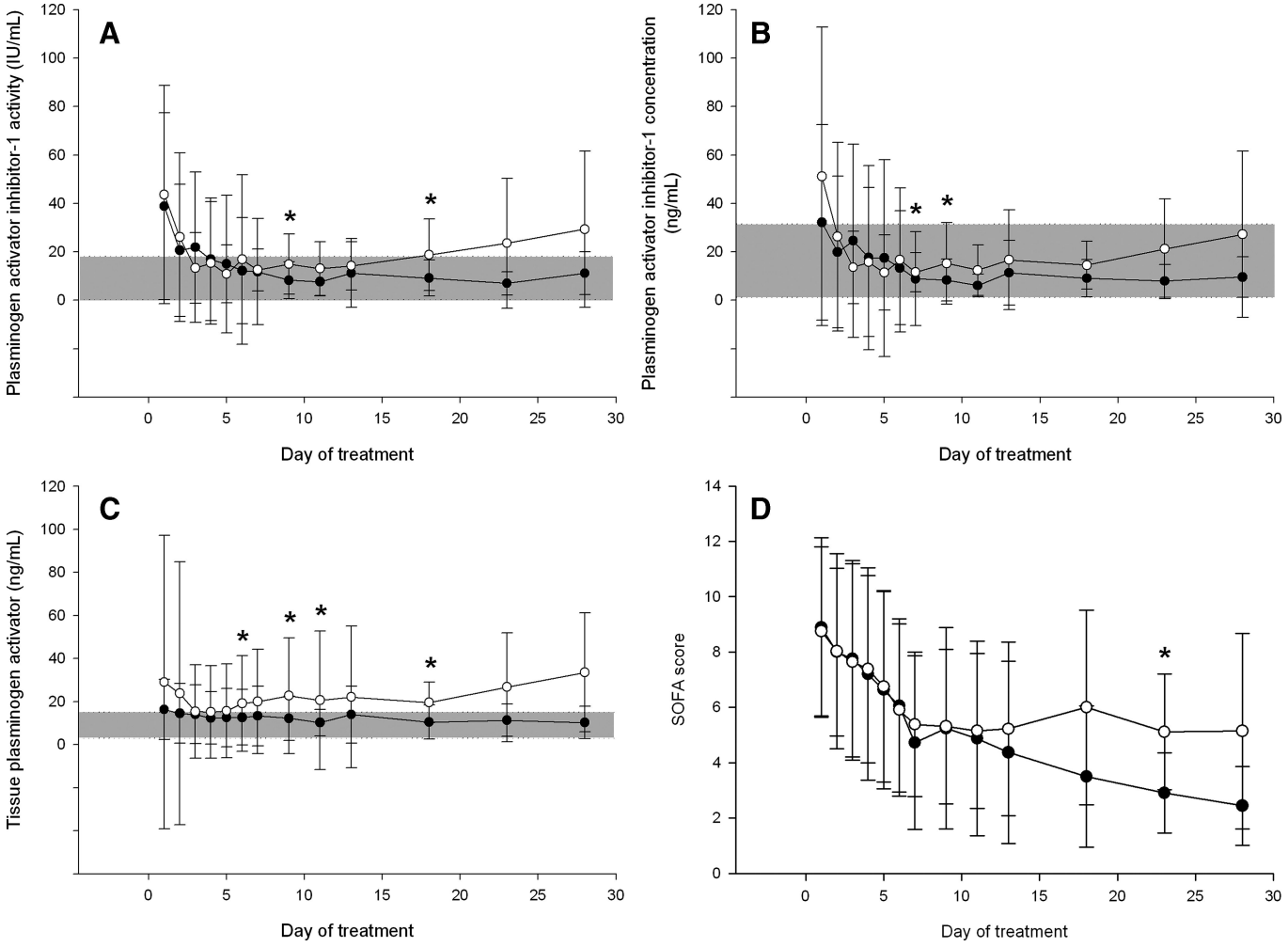

Figure 4. Time course of plasminogen activator inhibitor (PAI)-1 activity (*A*, trajectory difference: $p < 0.001$), PAI-1 concentration (*B*, trajectory difference: $p = 0.004$), tissue plasminogen activator (*C*, trajectory difference: $p = 0.01$), and Sepsis-related Organ Failure Assessment (*SOFA*) scores (*D*, trajectory difference: $p = 0.03$) in the treatment (*closed circles*) and control groups (*open circles*) (mean ± SD). *p* values refers to the trajectory >28 days and not to the differences of means at any given time point (mixed model for repeated measurements). The *asterisks* indicate statistical differences in the means of control and treatment subjects at that study day. The *shaded areas* in each panel indicate the normal range (up to the 95th percentile) used in the central laboratory where all samples were analyzed. Note that the immunoassay of tissue plasminogen activator (tPA) measures, to a large extent, circulating complexes between tPA and PAI-1. Consequently, increased concentration of tPA antigen indicate a reduced rather than increased fibrinolysis (30).

Clinical interventions specifically aiming at the fibrinolytic pathway in sepsis are lacking. In fact, most interventional studies in sepsis aimed at suppressing inflammation (8–14) or coagulation (15). These approaches may, at best, prevent progression of the disease by limiting further generation of microthrombi but are not likely to resolve already-established alterations. Reactivation of fibrinolysis, on the other hand, may achieve this goal. In this study, after several days, patients assigned to the tight glycemic control group tended to have lower morbidity than conventionally treated patients. The time lag was similar to the one required for PAI-1 concentration/activity to decrease. The slight unbalance of PAI-1 concentration (but not activity), age, and sex observed at the baseline between the two groups should not affect the overall results. In fact, although age is reported as a factor increasing PAI-1 concentration (40), in our population, at entry, we could not find any correlation between PAI-1 concentration or activity and age ($r^2 = .01$, $p = 0.38$ and $r^2 = .001$, $p = 0.82$, respectively). On the other hand, the influence of sex on PAI-1 concentration is controversial (41, 42) and—if present—should induce greater PAI-1 levels in women, as recently reported in a large series (43). Indeed, because in the control group, fewer women were included and patients were older, the effects of age and sex should balance each other. Furthermore, the slight individual differences in PAI-1 concentrations observed at study entry were taken into account in the analysis by including baseline PAI-1 concentration as a covariate in the statistical model. Our result suggests a small benefit of tight glycemic control, which seems time-dependent, as previously described in a large population of medical patients (44). Tight glycemic control is not an easy task. As shown in Figure 3*B*, there was a considerable frequency of hypoglycemic episodes. Although the rate of severe hypoglycemic episodes (glycemia <40 mg/dL) was similar in both groups, milder hypoglycemic episodes (glycemia <80 mg/dL) were more frequent in the tight glycemic control group. Blood glucose was tested every 4 hours during the study, as was done by Van den Berghe et al (19, 44), obtain-

ing similar glycemic control. It is likely, however, that if tests are done less frequently or not according to a predetermined protocol, the frequency and severity of hypoglycemic episodes may outweigh the benefits of the tight glycemic control strategy (21).

CONCLUSIONS

In conclusion, our data underline the importance of inhibition of fibrinolysis in sepsis. Tight glycemic control seems to be a potentially effective strategy for reactivating the fibrinolytic pathway. Alternative specific approaches targeted at the fibrinolytic pathway might also be considered for the fraction of patients in whom fibrinolysis is actually inhibited.

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